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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/709,170	11/10/2000	Raymond P. Warrell	10412-025	4982

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/709,170	WARRELL ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23 and 29-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 29-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicants Amendment and Remarks filed October 25, 2004.

Claims 1-23 and 29-33 are pending in the instant application.

Claims 1-23 and 29-33 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

It is noted that not all claims have a proper claim identifier as required under 37 CFR § 1.121. For example, claim 13 has been identified as "previously amended" where there appears to be no claim amendment to claim 13. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of ***treating*** cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg daily in one or more cycles of therapy, each cycle of therapy consisting of 2 to 13 days, does not reasonably provide enablement for a method of ***preventing*** cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg daily in one or more cycles of therapy, each cycle

of therapy consisting of 2 to 13 days. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This is a scope enablement rejection.

In regards to the method of preventing cancer in a human comprising administering a bcl-2 antisense oligonucleotide, as recited in the instant claims, the Applicant has not shown that cancer in a human could be prevented by administration of an oligonucleotide targeting bcl-2 mRNA. In addition, the Applicant does not disclose how the compositions are to be used in order to *prevent* cancer. It is not clear from the specification, that in order for prevention of cancer, whether the patient is potentially prone for cancer or whether a recurrence is being prevented. Is the therapy to prevent recited here started months ahead or days ahead of a probable expectation of cancer? Is there a particular amount of the formulation that needs to be administered? Is a particular treatment regimen necessary? How long must such a treatment continue in order to prevent cancer? Further, Applicant has only shown that one of skill in the art would expect the incidence of cancer to be reduced, not completely prevented. The prior art provides ample evidence for treatment of lymphomas via bcl-2 antisense (see Webb et al., 1997 The Lancet, Vol. 349:1137-1141; Cotter et al., 1999 Biochimica et Biophysica Acta 1489:97-106; Waters et al., 2000 Journal of Clinical Oncology, Vol. 18:1812-1823; Morris et al., 1999 Proceedings of the American Society of Clinical Oncology, Vol. 18:323a; and Jansen et al., 1999 Proceedings of the American Society of Clinical Oncology, Vol. 19:531a). However the prior art does not show the prevention of cancer or how one would prevent cancer via bcl-2 antisense. The instant specification does not show more than the prior art, therefore, one is left with undue trial and error experimentation to practice the instant invention.

In view of the lack of guidance provided in the specification as filed, the level of unpredictability in the art in regards to methods of prevention of cancer and antisense therapy, and the breadth of the given claims, it is concluded that undue experimentation would be required to practice the invention throughout the full scope of the claims, and therefore the invention is not fully enabled.

Claim Rejections - 35 USC § 102

In the previous office action mailed July 26, 2004, claims 1, 4, 5, and 13-18 were rejected under 35 U.S.C. 102(b) as being anticipated by Webb et al. (The Lancet, 1997 Vol. 349:1137-1141). **This rejection is withdrawn** in view of the Examiner's previous position that the claims recited the phrase "consisting essentially of". The Examiner has misinterpreted the claims as reciting, "consisting essentially of", where they actually recite, "consisting of". In view of this misinterpretation, the previous Office Action mailed July 26, 2004 construed the claims as equivalent to "comprising." This broad interpretation of the claims was an error on the Examiners part as the claims clearly recite, "consisting of" and not "consisting essentially of" and thus the claims excludes any element, step, or ingredient not specified in the claims. Therefore, the Examiner's request that Applicant show that the introduction of the additional steps or components disclosed by Webb et al. would materially change the characteristics of the invention is **withdrawn.**

However after careful reconsideration of the claims, claims 1-5 and 13-18 are rejected as follows:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 and 13-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Webb et al. (The Lancet, 1997 Vol. 349:1137-1141).

Claim 1 is drawn to a method of treating cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg daily in one or more cycles of therapy, each cycle of therapy consisting of 2 to 13 days. Claims 2 and 3 are dependent on claim 1 and include all the limitations of claim 1, with the further limitations wherein one or more cycles of therapy consist of 3 to 9 days; and wherein one or more cycles of therapy consist of 4 to 7 days. Claims 4 and 5 are dependent on claim 1 and include all the limitations of claim 1, with the further limitations comprising administering 4 to 9 or 5 to 7 mg/kd/day of the bcl-2 antisense oligonucleotide. Claims 13-18 are dependent on claim 1 and include all the limitations of claim 1, with the further limitations wherein said administration is a specific administration, wherein said cancer is a specific cancer, and wherein said antisense comprises at least two phosphorothioate linkages and is SEQ ID NO:17.

Webb et al. disclose treating human patients with non-Hodgkin's lymphoma with a daily subcutaneous infusion of an 18-base, fully phosphorothioated antisense oligonucleotide for 14 days (see page 1137, Methods). It is noted that the phosphorothioated antisense oligonucleotide disclosed by Webb et al. is identical to SEQ ID NO:17 of the instant invention. Webb et al. further disclose the daily dose of bcl-2 antisense was increased incrementally from 4.6 mg/m^2 to 73.6 mg/m^2 for 14 days (see page 1137, Findings). The issue at hand is the interpretation of the term "cycle of therapy". The Examiner has defined "cycle" according to Applicant's Specification at page 7, lines 28-35 where it recites, "cycle" referes to a period during which a single therapeutic or sequence of therapeutics is administered. Webb et al. teach a daily subcutaneous infusion of an 18-base, fully phosphorothioated antisense oligonucleotide for 14 days. This teaching is interpreted by the Examiner to consist of two cycles of therapy, each cycle of therapy consisting of 7 days. It is noted that this example reads on each cycle of therapy consisting of 2 to 13 days, 3 to 9 days, or 4 to 7 days, as recited in claims 1-3.

Therefore, "cycle" as recited by Applican'ts specification, is broadly defined to encompass the cycles of therapy taught by Webb et al. It is noted that using the defined meaning of the term "cycle" as recited in the instant specification at page 7, lines 28-35, the two cycles of therapy, each cycle of therapy consisting of 7 days, taught by Webb et al. are not excluded from the cycle(s) of therapy recited in the instant claims.

Therefore, Webb et al. anticipate claims 1-5 and 13-18.

Claim Rejections - 35 USC § 103

In the previous office action mailed July 26, 2004, claims 1-23 were rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al. (The Lancet, 1997 Vol. 349:1137-1141) in view of Bennett et al. [U.S. Patent No: 6,214,986].

This rejection is withdrawn in view of the Examiner's previous position that the claims recited the phrase "consisting essentially of". The Examiner has misinterpreted the claims as reciting, "consisting essentially of", where they actually recite, "consisting of". In view of this misinterpretation, the previous Office Action mailed July 26, 2004 construed the claims as equivalent to "comprising." This broad interpretation of the claims was an error on the Examiner's behalf as the claims clearly recite, "consisting of" and not "consisting essentially of" and thus the claims excludes any element, step, or ingredient not specified in the claims.

Therefore, the Examiner's request that Applicant show that the introduction of the additional steps or components disclosed by Webb et al. would materially change the characteristics of the invention is **withdrawn.**

However after careful reconsideration of the claims, claims 1-23 are rejected as follows:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al. (The Lancet, 1997 Vol. 349:1137-1141) in view of Bennett et al. [U.S. Patent No: 6,214,986].

Claim 1 is drawn to a method of treating cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg daily in one or more cycles of therapy, each cycle of therapy consisting of 2 to 13 days. Claims 2-18 are dependent on claim 1 and include all the limitations of claim 1, with the further limitations wherein one or more cycles of therapy consist of 3 to 9 days; wherein one or more cycles of therapy consist of 4 to 7 days; wherein the bcl-2 antisense oligonucleotide is administered at a dose of 4 to 9 mg/kg/day; wherein the bcl-2 antisense oligonucleotide is administered at a dose of 5 to 7 mg/kg/day; and further comprises administering one or more cancer therapeutics. Claim 19 is drawn to a method of treating cancer in a human comprising administering one or more chemoagents and a bcl-2 antisense oligonucleotide, wherein the bcl-2 antisense oligonucleotide is administered at a dose of 0.01 to 50 mg/kg daily in one or more cycles of therapy, each cycle of therapy consisting of 2 to 13 days. Claims 20-23 are dependent on claim 19 and include all the limitations of claim 19, with the further limitations of specific chemoagents, and specific doses of chemoagents.

Webb et al. disclose treating human patients with non-Hodgkin's lymphoma with a daily subcutaneous infusion of an 18-base, fully phosphorothioated antisense oligonucleotide for 14 days (see page 1137, Methods). It is noted that the phosphorothioated antisense oligonucleotide

disclosed by Webb et al. is identical to SEQ ID NO:17 of the instant invention. Webb et al. further disclose the daily dose of bcl-2 antisense was increased incrementally from 4.6 mg/m^2 to 73.6 mg/m^2 for 14 days (see page 1137, Findings). The issue at hand is the interpretation of "cycle of therapy". The Examiner has defined "cycle" according to Applicant's Specification at page 7, lines 28-35 where it recites, "cycle" referes to a period during which a single therapeutic or sequence of therapeutics is administered. Webb et al. teach a daily subcutaneous infusion of an 18-base, fully phosphorothioated antisense oligonucleotide for 14 days. This teaching is interpreted by the Examiner to consist of two cycles of therapy, each cycle of therapy consisting of 7 days. It is noted that this example reads on each cycle of therapy consisting of 2 to 13 days, 3 to 9 days, or 4 to 7 days, as recited in claims 1-3.

Therefore, "cycle" as recited by Applican'ts specification, is broadly defined to encompass the cycles of therapy taught by Webb et al. It is noted that using the defined meaning of the term "cycle" as recited in the instant specification at page 7, lines 28-35, the cycles of therapy taught by Webb et al. are not excluded from the cycle(s) of therapy recited in the instant claims.

Webb et al. do not teach wherein the bcl-2 antisense therapy further comprises administering one or more cancer therapeutics.

Bennett et al. teach the antisense modulation of bcl-x expression using therapeutic compositions comprising antisense nucleic acids. Bennett et al. also teach "the formulation of therapeutic compositions and their subsequent administration is believed to be within the skill of those in the art. Dosing is dependent on severity and responsiveness of the disease state to be treated, with the course of treatment lasting from several days to several months, or until a cure

is effected or a diminution of the disease state is achieved. Optimal dosing schedules can be calculated from measurements of drug accumulation in the body of the patient. Persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates. Optimum dosages may vary depending on the relative potency of individual oligonucleotides, and can generally be estimated based on EC_{50s} found to be effective in *in vitro* and *in vivo* animal models. In general, dosage is from 0.01 μg to 100 g per kg of body weight, and may be given once or more daily, weekly, monthly or yearly, or even once every 2 to 20 years. Persons of ordinary skill in the art can easily estimate repetition rates for dosing based on measure residence times and concentrations of the drug in bodily fluids or tissues" (see columns 16-17, last and first paragraphs, respectively). Bennett et al. also teach bcl antisense oligonucleotides are administered with one or more cancer therapeutics, including doxorubicin, 5-fluorouracil (5-FU), etoposide, and cisplatin, for example (see column 16, lines 28-52). Bennett et al. teach bcl antisense oligonucleotides are administered with prodrugs (see columns 11 and 12, last and first paragraphs, respectively).

It would have been obvious to one of ordinary skill in the art to devise a method of treating cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg daily in one or more cycles of therapy, each cycle of therapy consisting of 2 to 13 days, 3 to 9 days, or 4 to 7 days as taught by Webb et al. It would have been obvious to vary the antisense oligonucleotide dosage amount since it is routine and well known in the art to determine optimum dosages, dosing methodologies, and repetition rates based on measured residence times and concentrations of the drug in bodily fluids or tissues. It also would have been obvious to vary the antisense oligonucleotide dosage amount since Bennett et al. teach, in

general, dosage is from 0.01 μg to 100 g per kg of body weight, and may be given once or more daily, weekly, monthly or yearly, or even once every 2 to 20 years. It would have been further obvious to administer antisense therapy further comprising administering one or more cancer therapeutics or chemoagents as taught by Bennett et al. It would have been further obvious to administer antisense therapy further comprising administering one or more cancer therapeutics or chemoagents since it is routine and well known in the art that combination therapy is an effective approach for cancer treatment.

One skilled in the art would have been motivated to devise a method of treating cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg daily in one or more cycles of therapy, each cycle of therapy consisting of 2 to 13 days, 3 to 9 days, or 4 to 7 days because Webb et al. explicitly teaches this is an effective means of treating human patients with non-Hodgkin's lymphoma. One of ordinary skill in the art would be motivated to vary the antisense oligonucleotide dosage amount since Bennett et al. teach persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates of an antisense drug.

Therefore, the invention of claims 1-23 would have been obvious to one of ordinary skill in the art, as a whole, at the time the instant invention was made.

Response to Arguments

It is noted that in the previous Office Action mailed July 16, 2004, claims 1-23 were rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al., (The Lancet, 1997 Vol. 349:1137-1141) in view of Bennett et al. [U.S. Patent No: 6,214,986].

In response to this rejection, Applicants argue that while the methods for determining doses and treatment schedules are well known, the particular treatment schedule or dose that will be effective for any given drug is not known until it is discovered using these conventional methods. Applicants further argue that Bennett et al. is a general description relating to how dosages, treatment schedules and dosage forms are determined as is no more than an invitation to experiment. Applicants further argue that the antisense drug of Bennett et al. is different from Applicants' bcl-2 antisense drug and thus any specifics about dosages and treatment schedules for antisense to bcl-x do not suggest anything about appropriate dosages and treatment schedules for the claimed bcl-2 antisense. Applicants contend that the references of Webb et al. and Bennett et al. do not create any expectation that an attempt to modify the treatment schedule taught by Webb et al. by experimenting with a wide variety of alternative treatment schedules as suggested by Bennett et al. would result in Applicants' invention, i.e., successful administration of a bcl-2 antisense drug in 2 to 13 day cycles.

Applicant's arguments have been fully considered, but are not found persuasive because Applicant argues against the references individually, but must consider the rejection based upon the combination of the references. *See*, MPEP 2145. First, Webb et al. clearly teach successful administration of a bcl-2 antisense drug in 2 to 13 day cycles. Second, Bennett et al. provide clear motivation to modify the treatment schedule taught by Webb et al. to determine optimum dosing schedules. For example, Bennett et al. teach, "In general, dosage is from 0.01 μg to 100 g per kg of body weight, and may be given once or more daily, weekly, monthly or yearly, or even once every 2 to 20 years. Persons of ordinary skill in the art can easily estimate repetition rates for dosing based on measure residence times and concentrations of the drug in bodily fluids or

tissues" (see columns 16-17, last and first paragraphs, respectively). Besides, and as Applicants have pointed out in their arguments above, "methods for determining doses and treatment schedules are well known". Although the antisense drug of Bennett et al. is different from Applicants' bcl-2 antisense drug, Bennett et al. provide clear motivation to determine appropriate dosages and treatment schedules of an antisense drug, which is very similar in size and structure as Applicants bcl-2 antisense drug. Applicant's would be able to use this motivation, and reasonably expect to be successful, to determine appropriate dosages and treatment schedules for their bcl-2 antisense drug of the instant invention.

Therefore, the instant invention would have been prima facie obvious to one of ordinary skill in the art at the time of filing.

In the previous office action mailed July 26, 2004, claims 29-33 were rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al., (The Lancet, 1997 Vol. 349:1137-1141) in view of Bennett et al. [U.S. Patent No: 6,214,986]. **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed July 26, 2004.

Response to Arguments

In response to this rejection, Applicants argue that Bennett et al. is a general description relating to how dosages, treatment schedules and dosage forms are determined. Applicants contend that Bennett et al. is no more than an invitation to experiment and in no way suggests

that the 14-day treatment cycle of bcl-2 antisense taught by Webb et al. can be successfully modified to a 2 to 13 day treatment cycle, as presently claimed.

In argument has been fully considered, but is not found persuasive because Applicant argues against the references individually, but must consider the rejection based upon the combination of the references. *See*, MPEP 2145. Webb et al. clearly teach successful administration of a bcl-2 antisense drug in 2 to 13 day cycles. Bennett et al. was relied upon to teach bcl antisense oligonucleotides are administered with one or more cancer therapeutics (see column 16, lines 28-52).

Therefore, one of skill in the art would have been motivated to administer the pharmaceutical comprising a bcl-2 antisense oligonucleotide of the instant invention in combination with a cancer therapeutic agent since it is routine and well known in the art that combination therapy is an effective approach for cancer treatment and since Bennett et al. explicitly teach bcl antisense oligonucleotides are administered with one or more cancer therapeutics.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
January 4, 2005

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